

Reviewer A

The article was written on malignant phyllodes tumor with osteoclast-like giant cells.

Comment 1. The author should explain how to examine axillary nodes in patients with malignant PT in discussion.

Reply 1: Thank you for your valuable comments. The involvements of axillary nodes in malignant PTs are rare. So, routine axillary staging or dissection were not recommended according to the NCCN guideline. We had examined the axillary by using PET-CT and US before the operation. There were no signs of metastasis. So, we did not assess the axillary nodes in our case.

Changes in the text 1: We added some sentences to explain how to examine axillary nodes. (see Page 8, line19-21)

2. PTs with osteoclast-like giant cells have been very rare and relevance between clinical course and osteoclast-like giant cells has not been known well. So, we ask the author to show impact of osteoclast-like giant cells on clinical course in patients with other kind of tumors other than PT in discussion.

Reply 2: Unfortunately, there were no solid evidence to prove the relationship between the osteoclast-like giant cells and clinical course by now. But we found some studies or cases which indicate the possible relevance. We had described the osteoclast-like giant cells in breast cancer which showed the uncertain prognosis. We also found that tumors with OLGs may indicate the large tumor size, necrosis, and hemorrhage.

Changes in the text 3: We added some sentences to explain. (see Page 7, line 22, Page 8, line 1-5)

3. Sentences in line 15 to 20 in 5th page are difficult to understand.

Reply 3: This paragraph is the introduction of the diagnostic criteria of malignant PTs according to the WHO classification of breast tumors. I think it is important to declare for understanding the criteria of diagnosis. we will describe it specifically.

Changes in the text 3: We added some details to make it easy to understand. (see Page 6, Line

15-22)

4. English proofreading should be made.

Reply 4: We have modified the manuscript carefully.

Reviewer B

1. In page 4 of Case presentation, “She felt a great relief to her because she no longer had to carry the huge tumor.”; “Through extensive sampling, we had not found any heterologous sarcoma component such as osteosarcoma, liposarcoma or chondrosarcoma.”; “A timeline was shown in Figure 5 indicating the important event of the disease development.” can be deleted.

Reply 1: Thank you for your advises. I will explain why we wrote these sentences, the first sentence “She felt a great relief to her because she no longer had to carry the huge tumor.”, by CARE checklist demand, we use this sentence to describe patient’s perspective on the treatment they received. The topic number in CARE list is 12. We made a revise.

The second sentence “Through extensive sampling, we had not found any heterologous sarcoma component such as osteosarcoma, liposarcoma or chondrosarcoma.”, we want to emphasize the sampling procedure should be diligent. And the types of stroma cells were important characters of the tumor. So, we described that no heterologous sarcoma components were found. The stroma composed almost of non-specific high-grade spindle-like sarcomatous component. We made a revise.

The third sentence “A timeline was shown in Figure 5 indicating the important event of the disease development.”. The CARE list demands a timeline in the manuscript, so we added it literally.

Changes in the text 1: We have modified our text as advised. (see Page 4, line 18, Page 5, line 4-8, Page 5, line 18-19)

2. In Discussion, page 6, “Autologous skin grafts are an efficient and way for large defects caused by the resection of large tumors” -> For the safe margin reason, PM muscle may be resected, and skin graft reconstruction may be partial loss because of poor wound base sometimes. -> local flap or free flap reconstruction for the defect after mastectomy is more appropriated

Reply 2: I totally agree with your opinions. And your expression is accurate and comprehensive. I will add the discussion about this.

Changes in the text 2: We have modified our text as advised. (see Page 9, line 1-3)

3. VAC for post-graft care is one good option in this patient.

Reply 3: Thank you for your comments. VAC was commonly used for wounds of varieties parts of the body at our hospital.

Changes in the text 3: None.

4. Postoperative radiation therapy (RT) is suggested if tumor base or margin is not free.

Reply 4: Studies showed the first choice for positive margin is re-excision. When patient cannot get a sufficient negative margin (less than 1cm) adjuvant RT is recommend decreasing local recurrence rate.

Changes in the text 4: (see Page 8, line 15-19)

5. In conclusion, page 7, "OLGCs were uncommonly found by pathology. Significances of these cells is not clear yet. They may be associated with prognosis in malignant tumors." -> reference?

Reply 5: Through the discussion above we made another conclusion that the characteristics of malignant PTs with OLGCs characteristic. We think the sentence was inappropriate in the conclusion. So, we have deleted this sentence in conclusion. And we made a revise.

Changes in the text 5: We have modified out text. (see Page9, line 18-20)

6. The treatment of post-operative R/T or C/T will be changed or not in OLGCs?

Reply 6: The prognosis of the malignant phyllodes tumors with OLGCs is unclear yet and there is no evidence suggest that RT or CT will be changed in malignant PTs with OLGCs.

Changes in the text: None.

Reviewer C

Histopathological diagnosis of breast spindle-cell tumors is often difficult. Usual differential dianoses include spindle cell carcinoma, malignant phyllodes tumor, and other sarcomas. In the context of the presented case, the diagnosis of phyllodes tumor requires histological identification of leaf-like structures characteristic of phyllodes tumors (or maybe appropriate genetic changes). The information provided in the manuscript is insufficient for the histological

diagnosis of phyllodes tumor.

Though I believe that osteoclast-like giant cells in phyllodes tumors are not so uncommon as the authors state (see Figure 4 in Tan et al "Phyllodes tumours of the breast: a consensus review" *Histopathology*. 2016 Jan;68(1):5-21.), it is true that the literature on this subject is scarce.

1. Language editing is strongly recommended.

Reply 1: Thank you for your advice. We have edited our language carefully.

Changes in the text 1: The text have been edited.

2. p317 “rare cases... “ Citation needed (eg. Ref 7?)

Reply 2: As you stated above, we also believed that OLGs can be seen not only in malignant PTs but also in varieties of cancers. And I have also read the paper entitled "Phyllodes tumours of the breast: a consensus review". But we don't know how often do they occur in the malignant PTs. Tumors with OLGs may have something in common. we added some details to state our viewpoint.

We added a reference as advised. Authors of the reference described that they reported the first case of malignant PTs with OLGs in 2007. Though there were several cases were reported before and after, I think it is still rare in the literature.

Changes in the text 2: We have modified our text. (see Page 3, line 9)

3. p419 “Multiple vessel epithelial cells” The meaning of this phrase is not clear to the present reviewer. Maybe “endothelial cells”?

Reply 3: Thank you for pointing out the error. We put that in another way.

Changes in the text 3: We changed the word as advised. (see Page 5 line 4)

4. p417 “the diagnosis...” As we stated above, the information provided is insufficient for the diagnosis of phyllodes tumor.

Reply 4: Thanks for your valuable suggestion and comments. Indeed, the malignant PTs are difficult to identified from other spindle-like tumors. Diligent sampling was needed identifying from other tumors. Firstly, The clinical characteristics as important as pathology in diagnosis. For macroscopic appearance aspect, size of PTs is large, speed of growth is fast, and it had a

sarcomatoid growth pattern. Clinically, the tumor was malignant in our case. Pathologically, PTs are biphasic tumors which are characterized by two different cellular elements. Benign epithelium and hypercellular stroma must exist at the same time. We have found typical leaflike architecture and sarcomatoid stroma at the same time(Figure 4). As for differential diagnosis, The spindle cell metaplastic carcinoma must be excluded firstly when making a diagnosis of spindle-like tumors. Most of them show CK(+) and P63(+), in our case P63 and CK AE1/AE3 are negative. We did not find any heterologous sarcoma component such as osteosarcoma, liposarcoma or chondrosarcoma. The stroma composed almost of non-specific high grade spindle-like sarcomatous component. Above all, we confirmed the diagnosis.

Changes in the text 4:(see Page 4, line 20-22, Page 5, line 1-10, Figure 4C)

5. p5116 “polymorphism” should be “pleomorphism”

Reply : We changed the word as advised.

Changes in the text:(see Page 5, line 1)

6. p5117 “epidermis” should be “epithelium”

Reply : We changed the word as advised.

Changes in the text:(see Page 6, line 20)

7. p5118 “0.5 mm” This is corrected at the publisher’s web page. See the link below. The correct figure is “0.2”^[1]_[SEP] <https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Breast-Tumours-2019>

Reply : Thanks for careful checking. I had read the corrections of the book. And, we revised the 0.5mm to 0.2mm

Changes in the text:(see Page 6, line21)

8. p619 “merely” Meaning unclear. Perhaps “rarely”?

Reply : We changed the word as advised.

Changes in the text:(see Page 8, line 7)

9. p6113 “whatever the pathology...” Meaning unclear.

Reply : To avoid the misunderstanding, we deleted the sentence.

Changes in the text:(see Page 8, line 14)